

# Understanding the influence of Lewis acids in the regioselectivity of the Diels–Alder reactions of 2-methoxy-5-methyl-1,4-benzoquinone: A DFT study

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## ABSTRACT

The mechanisms of the Diels–Alder (DA) reactions of 2-methoxy-5-methyl-1,4-benzoquinone **1** with 2-methyl-1,3-butadiene **2**, in the absence and in the presence of LA catalysts, have been studied using the DFT method at the B3LYP/6-31G(d) level of theory. The uncatalyzed DA reactions between **1** and **2** take place via synchronous concerted TSs. The large activation barrier as well as the low stereo and regioselectivity associated with the uncatalyzed process are in clear agreement with the non-polar character of the cycloaddition. Coordination of the LA catalysts, BF<sub>3</sub> or SnCl<sub>4</sub>, to the oxygen atoms of the benzoquinone **1** produces a large acceleration of the reaction, which can be associated with the large polar character of the cycloaddition. The different coordination modes of BF<sub>3</sub> and SnCl<sub>4</sub> LA catalysts to the oxygen atoms of benzoquinone **1** allow explaining the reverse *para/meta* regioselectivity observed in these LA-catalyzed DA reactions. The analysis based on the global and local electrophilicity indices of the reagents correctly explains the polar nature of the title reactions, as well as the change of regioselectivity experimentally observed.

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## 1. Introduction

The Diels–Alder (DA) reaction is a powerful tool employed frequently in the synthesis of six-membered ring systems with excellent regio and stereoselective control [1]. In this process a 1,3-diene reacts with an olefinic or acetylenic dienophile to form a six-member ring adduct. The usefulness of DA reactions arises from its versatility and from its remarkable stereochemistry. By varying the nature of the diene and dienophile many types of carbocyclic structure can be built up.

The use of quinones as dienophile component in DA reactions provides access to a range of structures that are part of the fundamental skeleton of natural products and biologically active molecules [2]. The effects of the substituents on the quinone system are important because they determine the regiochemistry of the DA reactions. Electron-releasing substituents effects, CH<sub>3</sub>O > CH<sub>3</sub>, on the quinone decrease the reactivity of the double bond to which they are attached. In addition, the methoxy group produces an influence on the orientation at the unsubstituted double bond [3]. The interactions between unsymmetrical dienes can give two isomeric cycloadduct, depending upon relative positions of the substituent in the cycloadduct. For 1-substituted dienes head-to-head interactions corresponds to *orto* channel and head-to-tail

interactions corresponds to *meta* channel. For 2-substituted dienes, head-to-head corresponds to *meta* channel and head-to-tail corresponds to *para* channel. This substitution usually directs the DA reaction with 2-substituted dienes to give the *para* cycloadducts.

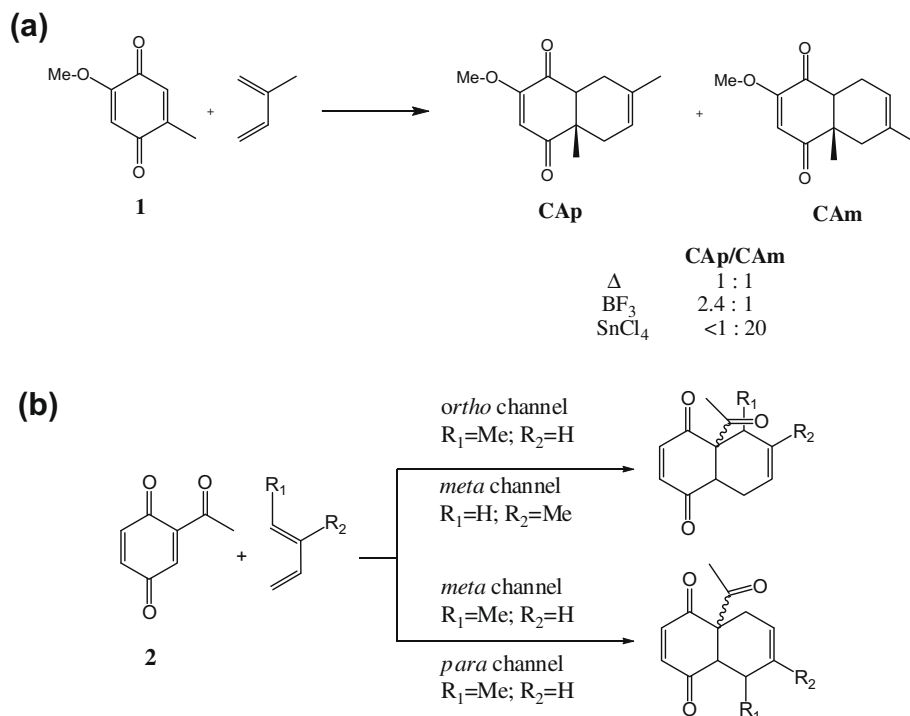
Tou and Reusch [4] reported that the regiochemistry of 2-methoxy-5-methyl-benzoquinone **1** with alkyl-substituted dienes like 2-methyl-1,3-butadiene **2** can be directed to favor either of the regioisomeric adducts by using appropriate Lewis acid (LA) catalysts (Scheme 1a). Thus, while the use of BF<sub>3</sub>·OEt<sub>2</sub> produce a 2.4:1 ratio of the *para/meta* regioisomeric cycloadducts, thereby indicating that this cycloaddition proceeds with very low regioselectivity; the use of SnCl<sub>4</sub> produces an inverse relationship with a higher regiochemistry in favor of the *meta* regioisomeric cycloadduct 1:20 *para/meta*. In absence of a LA, the *para* and *meta* cycloadducts are formed in a 1:1 ratio [4].

The activation energy associated to the DA reactions has been related with the polar character of the TS involved in such processes [5,6]. The characterization of the electrophilic/nucleophilic character of the reagents allows predicting the polar character of the reaction and in consequence the feasibility of the process. In this context, it is worth noting that the LA-catalyzed DA reactions take place through TSs with a larger zwitterionic character [7,8].

The global electrophilicity index  $\omega$  proposed by Parr et al. [9] has been used to classify the dienes and dienophiles currently used in DA reactions within a unique scale of electrophilicity [10,11].

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**Scheme 1.** (a) Regiochemistry of 2-methoxy-5-methyl-benzoquinone **1** with alkyl-substituted dienes as 2-methyl-1,3-butadiene **2** Ref. 4 (b) DA reactions of 2-acetyl-1,4-benzoquinone **3** with methyl substituted 1,3-butadienes. Regiochemical channels.

A good correlation between the difference in electrophilicity of the diene and dienophile pair,  $\Delta\omega$ , and the feasibility of the cycloaddition was found. A high electrophilicity at the dienophile and a high nucleophilicity at the diene will in general result in a highly polar transition state, associated with a favorable diene – dienophile interaction, thereby facilitating the cycloaddition [10]. In addition, the static charge transfer (CT) model proposed by Pearson [12] gave a good correlations with the actual CT found at the corresponding highly asynchronous TSs [10]. Therefore,  $\Delta\omega$  for a diene/dienophile pair is a valuable tool to predict the polar character of a DA reaction. In addition, the local counterpart condensed to atom  $k$ ,  $\omega_k$  [13], has been found to be a useful tool that correctly explains the regioselectivity of the polar DA reactions. The local electrophilicity together with the Fukui functions for electrophilic attack, [14]  $f_k^-$ , allow the identification of the most electrophilic and nucleophilic centers in the reactants [13].

Recently, we have studied the DA reactions of 2-acetyl-1,4-benzoquinone **3**, an electrophilically activated benzoquinone, with methyl substituted 1,3-butadienes [15] (Scheme 1b). These reactions were characterized by the nucleophilic attack of the unsubstituted ends of 1,3-dienes to the  $\beta$  conjugated position of the 2-acetyl-1,4-benzoquinone followed by a ring-closure. These DA reactions have low activation energies, between 9.5 and 14.8 kcal/mol (B3LYP/6-31G(d)), [16] and a large *endo* selectivity.

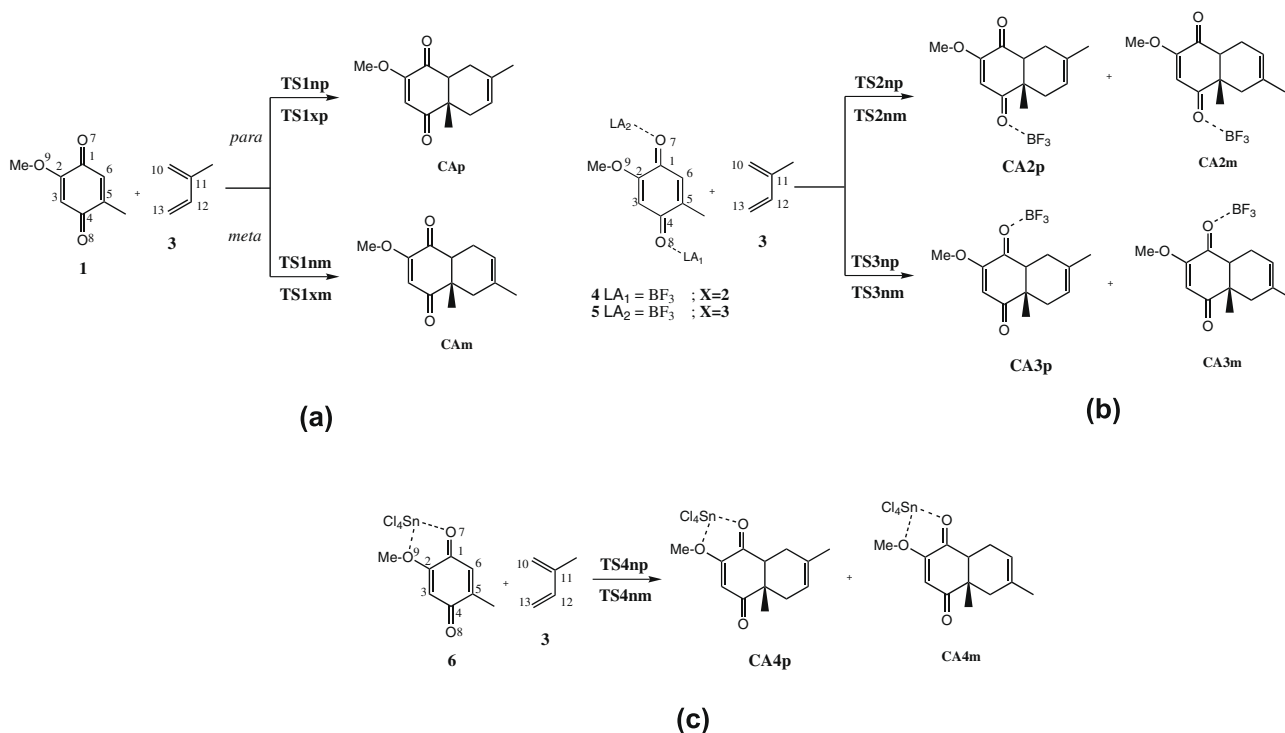
In this work we present a theoretical study about the mechanisms of the DA reactions of 2-methoxy-5-methyl-benzoquinone **1** with 2-methyl-1,3-butadiene **2**, in the absence and in the presence of LA catalysts,  $\text{BF}_3$  and  $\text{SnCl}_4$  (see Scheme 2). We first make a reactivity analysis based on static reactivity indices to discuss the origin of the polar character and the regioselectivity of these cycloadditions. Then, the mechanism of DA reactions between the benzoquinone **1** and the 2-methylbutadiene **2** in absence and in the presence of LA catalysts coordinated to different positions of the benzoquinone **1** is discussed. The purpose of our work is to contribute to a better understanding of the changes in the reg-

iochemistry due to different modes of LA coordination in these DA reactions and to shed some light on the mechanistic details of these polar cycloadditions.

## 2. Methodology

DFT calculations were carried out using the B3LYP [17,18] exchange-correlation functional, together with the standard 6-31G(d) basis set [19] for hydrogen, carbon, oxygen, boron, fluorine and chlorine and the Hay–Wadt small-core effective core potential (ECP) including a double- $\xi$  valence basis set for Tin [20] (LandL2DZ keyword). The optimizations were carried out using the Bery analytical gradient optimization method. [21] The intrinsic reaction coordinate (IRC) [22] path was traced to check the energy profiles connecting each transition structure to the two associated minima of the proposed mechanism by using the second-order González–Schlegel integration method [23,24]. All calculations were carried out with the Gaussian 03 suite of programs [25]. The stationary points were characterized by frequency calculations. The electronic structures of TSs and ground states were analyzed in term of the bond orders (BO) [26] and the natural charges obtained from the natural bond orbital (NBO) method [27,28] at the same calculation level. Solvent effects were evaluated by performing single-point B3LYP/6-31G(d) calculations at the gas-phase stationary points involved in the reaction using the polarizable continuum model (PCM) of Tomasi's group [29,30]. Since the solvent is usually dichloromethane, we used a dielectric constant value  $\epsilon = 8.93$ .

Global reactivity indexes such as the electronic chemical potential,  $\mu$ , chemical hardness,  $\eta$ , and electrophilicity  $\omega$ , were approximated in terms of the one electron energies of the frontier molecular orbital (FMO) HOMO and LUMO,  $\epsilon_H$  and  $\epsilon_L$ , using the expressions  $\mu \approx (\epsilon_H + \epsilon_L)/2$  and  $\eta \approx (\epsilon_L - \epsilon_H)$  and  $\omega = \mu^2/2\eta$ , respectively, at the ground state of the molecules [32]. The local electrophilicity [10],  $\omega_k$ , condensed to atom  $k$  is easily obtained by



**Scheme 2.** (a) Regioisomeric channels of the uncatalyzed DA reaction between 2-methoxy-5-methyl-1,4-benzoquinone **1** and 2-methyl-1,3-butadiene **2**. Regioisomeric channels for (b) the catalyzed DA reaction between 2-methoxy-5-methyl-1,4-benzoquinone **1** and 2-methyl-1,3-butadiene **2** with the  $\text{BF}_3$  catalyst and (c) with the  $\text{SnCl}_4$  catalyst coordinated.

projecting the global quantity onto any atomic center  $k$  in the molecule by using the condensed electrophilic Fukui function [33],  $f_k^+$  at the B3LYP/6-31G(d) level. There results:  $\omega_k = \omega f_k^+$ .

The presence of the  $\text{BF}_3$  LA catalyst has been considered in two coordination modes: in **4** the coordination is at the carbonyl O9 oxygen while in **5** it is attached to the carbonyl O7 oxygen atom. For the  $\text{SnCl}_4$  LA catalyst only one coordination mode has been considered, namely double coordination to the carbonyl O9 and methoxy O8 oxygens in **6** (see Scheme 2c).

### 3. Results and discussion

#### 3.1. Global electrophilicity analysis

Recent studies carried out on DA reactions [5–8,15] have shown that the reactivity indices defined within the conceptual density functional theory [34,35] are powerful tools to study the polar character of the cycloaddition. In Table 1, we report the static global properties, namely, electronic chemical potential  $\mu$ , chemical hardness  $\eta$ , and global electrophilicity  $\omega$  for the system 1–2 and the LA coordinated systems **4–6**.

The electronic chemical potential of 2-methylbutadiene **2** ( $\mu = -0.1226$  au) is higher than that of benzoquinone **1** ( $\mu = -0.1848$  au), thereby indicating that along a polar DA reaction, the net CT will take place from the diene **2** toward the benzoquinone **1**, in qualitative agreement with the CT analysis performed at the TS structures (*vide infra*). Coordination of the LA catalysts,  $\text{BF}_3$  or  $\text{SnCl}_4$ , to the carbonyl oxygen atoms of benzoquinone **1** decreases the electronic chemical potential value of **1** to  $-0.2193$  au for **4**,  $-0.1980$  au for **5** and  $-0.2355$  au for **6**.

The electrophilicity of benzoquinone **1** is 3.21 eV, a value that falls within the range of strong electrophiles in the  $\omega$  scale. [10] Note that the electrophilicity of **1** is lower than that of 2-acetyl-1,4-benzoquinone **3** ( $\omega = 4.64$  eV) [15] probably as a consequence of the substitution by the electron-withdrawing acetyl group pres-

ent in **3** compared to the electron-releasing methoxy group in **1**. Coordination of  $\text{BF}_3$  to the carbonyl O9 oxygen in **4** increases the electrophilicity of **1** to 4.39 eV, while coordination to O7 oxygen in **5** results in an electrophilic activation to 3.87 eV. On the other hand, coordination of  $\text{SnCl}_4$  to carbonyl O7 and methoxy O8 oxygen atoms increases the electrophilicity of **6** to 6.42 eV due to the larger acid character of  $\text{SnCl}_4$ , and a decrease of the electron-releasing ability of the methoxy oxygen atom with the LA coordination. The difference in electrophilicity of the diene and dienophile pair  $\Delta\omega$  for DA reactions has been used to predict the polar character of the cycloadditions [10]. The  $\Delta\omega$  values for uncatalyzed DA reaction between **1** and **2** is 2.32 eV, while for the LA-catalyzed reactions, these values raise to 3.95 eV, 2.89 eV and 5.44 eV for **4**, **5** and **6**, respectively. The larger  $\Delta\omega$  values found for the LA-catalyzed DA reactions indicate that they will present

**Table 1**

Electronic chemical potential  $\mu$  (in a.u.), chemical hardness  $\eta$  (in a.u.) and global electrophilicity  $\omega$  (in eV) for **1–2** and the LA coordinated systems **4–6**, and local electrophilicity  $\omega_k$  (in eV) for **1** and **4–6**.

	$\mu$	$\eta$	$\omega$	$\omega_k$			
				C <sub>2</sub>	C <sub>3</sub>	C <sub>5</sub>	C <sub>6</sub>
<b>1</b>	-0.1848	0.1446	3.21	0.28	0.16	0.40	0.27
<b>4</b>	-0.2193	0.1325	4.93	0.51	0.10	0.47	0.47
<b>5</b>	-0.1980	0.1380	3.87	0.29	0.21	0.52	0.27
<b>6</b>	-0.2355	0.1176	6.42	0.38	0.47	0.93	0.27
<b>2</b>	-0.1226	0.2069	0.98				

a larger polar character at the TS. In addition, it may be anticipated that the DA reaction between **2** and **6** will present the largest polar character and the largest acceleration.

Recent studies on cycloadditions with a large polar character have shown that the analysis based on the local electrophilicity  $\omega_k$  [13] allows one to explain the regioselectivity experimentally observed. The analysis of local electrophilicity on benzoquinone **1** indicates that the C5 position is the more electrophilic center of the molecule ( $\omega_{C5} = 0.40$  eV). This result is not in agreement with the regioselectivity experimentally observed for uncatalyzed reaction (*vide infra*). However, coordination of **1** with  $\text{BF}_3$  in **4** produces a similar activation at C5 and C6 ( $\omega = 0.47$  eV), in good agreement with the low regioselectivity experimentally observed for this catalyzed DA reaction. On the other hand, the coordination at carbonyl O7 oxygen with  $\text{BF}_3$  in **5** and  $\text{SnCl}_4$  in **6** produces a large activation at C5 position ( $\omega_{C5} = 0.52$  eV and  $\omega_{C5} = 0.93$  eV) respectively. The regioselectivity predicted for **6** is in close agreement with the experiment.

### 3.2. Study of the uncatalyzed Diels–Alder reaction between 2-methoxy-5-methyl-1,4-benzoquinone **1** and 2-methylbutadiene **2**

The DA reaction between benzoquinone **1** and 2-methylbutadiene **2** can take place along four reactive channels: the two *endo* and *exo* stereoisomeric channels and the two *ortho* and *meta* regioselective channels. An exhaustive exploration of the PES for these DA reactions indicates that they are associated with concerted C–C bond-formation processes. One TS and the corresponding [4+2] cycloadduct associated with the four reactive channels was located and characterized (see Scheme 2a).

The total and relative energies corresponding to the stationary points associated with these reactive channels are summarized in Table 2. The activation barriers associated with the cycloaddition processes are 22.5 kcal/mol for **TS1np**, 24.3 kcal/mol for **TS1xp**, 22.8 kcal/mol for **TS1nm** and 24.3 kcal/mol for **TS1xm**. These energy results indicate that the *endo* approaches are 1.8 and 1.5 kcal/mol more favorable than the *exo* ones. On the other hand, the *ortho* and *meta* channels present almost similar activation energies, thereby correctly suggesting a 1:1 product distribution. Therefore, the uncatalyzed DA reaction between **1** and **2** presents poor regioselectivity. The more favorable channel via **TS1np** is only 2.3 kcal/mol lesser in energy than that calculated for the unfavorable DA reaction between butadiene and ethylene [36]. Note that the activation barrier associated with the DA reaction between 2-acetyl-1,4-benzoquinone **3**, and **2** is 11.6 kcal/mol; [15] therefore the substitution by the electron-withdrawing acetyl group present in **3** by an electron-releasing methoxy group in **1** produces a dramatic increase in activation energy compared to the DA reaction of **1** with **2**.

The geometries, lengths of the forming bonds and bond order of the TSs of the DA reaction between **1** and **2** are shown in Fig. 1. The

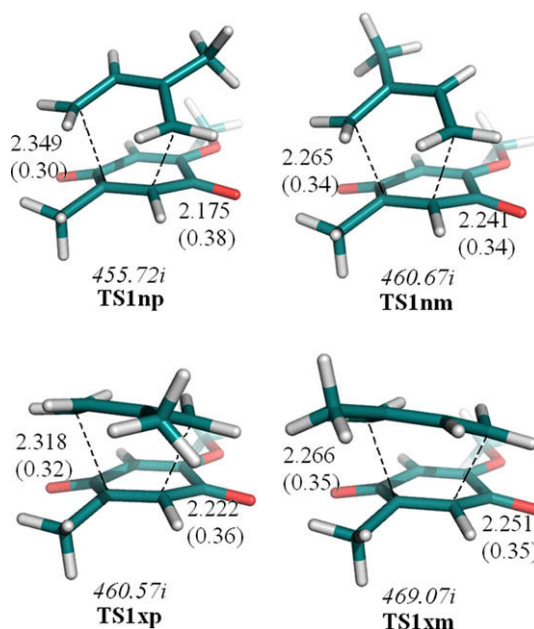


Fig. 1. Geometries of transition states of the DA reaction between 2-methoxy-5-methyl-1,4-benzoquinone **1** and 2-methyl-1,3-butadiene **2**. The imaginary frequencies are given in cm<sup>-1</sup> and bond distances in Å units. Bond order values are given in parenthesis.

extent of the asynchronicity of bond-formation can be measured by means of the difference between the lengths of the two  $\sigma$  bonds that are being formed in the reaction, i.e.,  $\Delta d = d(\text{C5}–\text{C13}) – d(\text{C6}–\text{C10})$  at the *para* TSs and  $\Delta d = d(\text{C5}–\text{C10}) – d(\text{C6}–\text{C13})$  at the *meta* TSs. The values calculated at the TSs are 0.17 at **TS1np** and 0.09 at **TS1xp**, 0.02 at **TS1nm** and 0.01 at **TS1xm**. These rather low values point out to the low asynchronicity that is present in concerted processes. These results indicate that these TSs correspond to concerted but slightly asynchronous bond-formation processes.

The natural population analysis (NPA) allows evaluating the CT along these cycloadditions [10]. The natural charges at the TSs appear shared between the donor 2-methylbutadiene **2** and the acceptor benzoquinone **1** frameworks. The CT from the diene **2** to **1** at the TSs are 0.18e at **TS1np** and **TS1nm**, 0.16e at **TS1xp** and 0.17e at **TS1nm**. These values are slightly larger than those obtained at the TS associated with the non-polar DA reaction between butadiene/acroleine, 0.11e [10] and account for the large activation energy associated with these DA reactions.

### 3.3. Study of LA-catalyzed Diels–Alder reactions between 2-methoxy-5-methyl-1,4-benzoquinone **1** and 2-methylbutadiene **2**

Previous studies on benzoquinones bearing electron-withdrawing substituents have shown that these DA reactions present *endo* selectivity. [15] In addition, the *endo* and *exo* stereoisomeric reactive channels leading to the same regioisomeric cycloadduct. In consequence, for the catalyzed DA reactions only the *endo* approaches modes of the diene system of **2** over the benzoquinone system of **1** have been studied. For DA reactions catalyzed with  $\text{BF}_3$ , two coordination modes of the LA to each one of the two carbonyl oxygen atoms have been considered (see Scheme 2b). The total and relative energies associated with the processes are summarized in Table 3. The activation barriers associated with the  $\text{BF}_3$  catalyzed DA reactions are 13.9 kcal/mol for **TS2np** and 13.6 kcal/mol for **TS2nm**, 15.8 kcal/mol for **TS3np** and 16.0 kcal/mol for **TS3nm**. Therefore, a large acceleration with the LA coordination is found for the catalyzed process as a consequence of the enhancement in electrophilicity of **4** and **5** relative to **1**. These en-

Table 2

B3LYP/6–31G(d) total energies ( $E$  in a.u.), relative<sup>a</sup> energies ( $\Delta E$  in kcal/mol), in vacuum and in dichloromethane, of the stationary points for the DA reactions of 2-methoxy-5-methyl-1,4-benzoquinone **1** with the 2-methyl-1,3-butadienes **2**.

	$E$	$\Delta E$	$E_{\text{solv}}$	$\Delta E_{\text{solv}}$
1+2	–730.611835		–730.624553	
TS1np	–730.575479	22.5	–730.589364	22.0
TS1xp	–730.573138	24.3	–730.586467	23.9
CAp	–730.656975	–28.3	–730.668360	–27.5
TS1nm	–730.576022	22.8	–730.589617	21.9
TS1xm	–730.573125	24.3	–730.586348	23.9
CAm	–730.656347	–27.9	–730.667703	–27.1

<sup>a</sup> Energy values relative to the separated reagents.

**Table 3**

B3LYP/6-31G(d) total energies ( $E$  in a.u.), relative<sup>a</sup> energies ( $\Delta E$  in kcal/mol), in vacuum and in dichloromethane, of the stationary points for the DA reactions of 2-methoxy-5-methyl-1,4-benzoquinone in presence of LA **4**, **5** and **6** with the 2-methyl-1,3-butadienes **2**.

	$E$	$\Delta E$	$E_{\text{solv}}$	$\Delta E_{\text{solv}}$
4 + 2	-1055.185649		-1055.203572	
TS2np	-1055.163413	13.9	-1055.183829	12.4
CA2p	-1055.233921	-30.2	-1055.250675	-39.5
TS2nm	-1055.163904	13.6	-1055.183511	12.6
CA2m	-1055.233687	-30.1	-1055.250541	-39.4
5 + 2	-1055.176265		-1055.189476	
TS3np	-1055.151012	15.8	-1055.173768	9.8
CA3p	-1055.221488	-28.4	-1055.233110	-27.4
TS3nm	-1055.150779	16.0	-1055.172713	10.5
CA3m	-1055.221788	-28.5	-1055.233233	-27.5
6 + 2	-2574.925740		-2574.947337	
TS4np	-2574.902321	14.7	-2574.928543	11.8
CA4p	-2574.968534	-13.6	-2574.986862	-24.8
TS4nm	-2574.904863	13.1	-2574.931321	10.0
CA4m	-2574.968763	-13.5	-2574.986988	-24.8

<sup>a</sup> Energy values relative to the separated reagents.

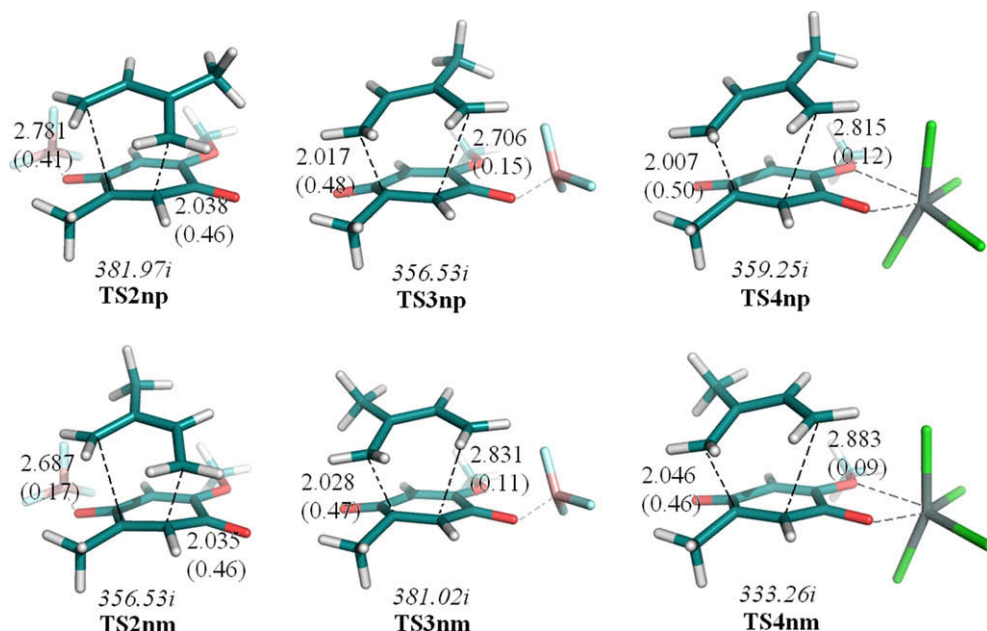
ergy barriers show that the coordination of  $\text{BF}_3$  to the carbonyl O9 oxygen at **4** is more favored than coordination at the carbonyl O7 oxygen in **5**, in good agreement with the larger electrophilicity activation predicted for the LA complex **4** than that for the LA complex **5**. The effect of the LA catalyst is therefore revealed at the transition state structure. For instance, in the energy profile, complex **4** appears 5.9 kcal/mol below complex **5**. These energy results indicate that the reactive channels via **TS2np** and **TS2nm** are favored over those via **TS3np** and **TS3nm**. For the  $\text{SnCl}_4$  catalyzed DA reaction, the two *endo* regioisomeric channels were studied. The activation barriers are 14.7 kcal/mol for **TS4np** and 13.1 kcal/mol for **TS4nm**. A change of the regioselectivity is found with the coordination of Sn cation to the carbonyl O7 and methoxy O8 oxygen atoms. The activation barrier associated with **TS4nm** presents the lowest values of the LA-catalyzed DA reactions of the benzoquinone **1**, in good agreement again with the largest  $\Delta\omega$  found for  $\text{SnCl}_4$  catalyzed DA reaction.

The geometries, lengths of the forming bonds and bond order of the TSs associated with the DA reaction of the  $\text{BF}_3$  LA complexes **4** and **5** and  $\text{SnCl}_4$  LA complex **6** with the diene **2** are shown in Fig. 2. The extents of the asynchronicity on bond-formation at the TSs are 0.74 at **TS2np**, 0.64 at **TS2nm**, 0.68 at **TS3np**, 0.80 at **TS3nm**, 0.80 at **TS4np** and 0.83 at **TS4nm**. These large values point to highly asynchronous TSs associated with two-center additions. These results indicate that these TSs correspond to highly asynchronous bond-formation processes.

Finally, the CT at the TSs associated to the LA-catalyzed DA reactions are 0.33e at **TS2np**, 0.34e at **TS3np** and 0.39e at **TS4np**, for the *meta* TSs, the calculated CT are 0.30e at **TS2nm**, 0.37e at **TS3nm** and 0.41e at **TS4nm**. These values indicate that these structures have a large zwitterionic character. Coordination of the LAs to the benzoquinone **1** results in a large increase of the CT at the TSs as a consequence of the increase in electrophilicity of the corresponding LA complex. This behavior allows explaining the large acceleration observed in these polar DA reactions.

As these LA-catalyzed DA reactions have a polar character, and solvent can stabilize some species, solvent effects by dichloromethane were considered by means of single point energy calculations on the gas-phase optimized geometries using the PCM method [31]. Several studies devoted to polar DA reactions have indicated that the inclusion of solvent effects on the geometry optimization produce only minor changes relative to the gas-phase calculations [5,6]. The total and relative energies in dichloromethane are given in Tables 2 and 3, respectively. For the DA reaction between the benzoquinone **1** and 2-methylbutadiene **2** the decrease in activation barrier is only 0.5 kcal/mol. This marginal solvent effect on the activation barriers may be traced to the low polarity of the TSs (see Table 2).

As expected, a solvent polar effect will stabilize more effectively the TSs when this structure presents a polar character. Therefore, for the LA-catalyzed DA reactions solvent effects produce a large acceleration as a consequence of a larger stabilization of the polar TSs than reagents. These results are a consequence of the increase of the electrophilicity of benzoquinone **1** with the LA coordination. In addition, for the  $\text{BF}_3$  LA-catalyzed DA reaction of **1** inclusion of solvent effects produces an inversion of the gas-phase regioselectivity.



**Fig. 2.** Geometries of *endo* transition states of the DA reactions between 2-methoxy-5-methyl-1,4-benzoquinone with  $\text{BF}_3 \cdot \text{OEt}_2$  as LA **4**, **5** and with  $\text{SnCl}_4$  as LA **6** and 2-methyl-1,3-butadiene **2**. The imaginary frequencies are given in  $\text{cm}^{-1}$  and bond distances in Å units. Bond order values are given in parenthesis.

tivity, in clear agreement with the experimental result. In dichloromethane, **TS2np** is 0.2 kcal/mol lesser in energy than **TS2nm** as a consequence of a large solvation of the former. Note that even through in dichloromethane the activation barrier associated with **TS3np**, 9.8 kcal/mol, is lower than that for **TS2np**, 12.8 kcal/mol, the larger stability of complex **4** compared to complex **5**, –8.9 kcal/mol, causes the reaction channel to follow the pathway through **TS3np**. This result is in agreement with the Curtin–Hammett principle [37]

In summary in dichloromethane the  $\text{BF}_3$  catalyzed DA reaction presents a low *para* regioselectivity. However, the  $\text{SnCl}_4$  catalyzed DA reaction presents a large *meta* selectivity. An inversion of the regioselectivity with respect the  $\text{BF}_3$  catalyzed process is found in good agreement with the experimental results.

#### 4. Concluding remarks

The mechanisms of the Diels–Alder reactions of 2-methoxy-5-methyl-1,4-benzoquinone **1** with 2-methyl-1,3-butadiene **2**, in the absence and in the presence of LA catalysts have been studied using DFT method at the B3LYP/6-31G(d) level of theory. For the uncatalyzed reaction both *endo/exo* stereo and *para/meta* regioselectivity channels have been studied. These DA reactions take place via synchronous concerted TSs. The larger activation barrier associated with the uncatalyzed process is in good agreement with the non-polar character of the cycloaddition. The uncatalyzed reaction presents a low regioselectivity. Coordination of the LA catalysts,  $\text{BF}_3$  or  $\text{SnCl}_4$ , to the oxygen atoms of the benzoquinone **1** produces a large acceleration of the reaction, which can be associated with a larger polar character of the cycloaddition. The different coordination modes of the  $\text{BF}_3$  and  $\text{SnCl}_4$  LA catalysts to the benzoquinone **1** allow explaining the reverse *para/meta* regioselectivity observed in these LA-catalyzed DA reactions.

The theoretical results obtained may thus provide a useful tool for the interpretation of the reaction mechanisms. The analysis based on the electrophilicity index of reagents correctly explains the polar nature of the LA-catalyzed DA reactions. The strong electrophilic character of LA complexes of the methoxybenzoquinone **1** accounts for the large acceleration found in these DA reactions. Finally, the analysis based on the local electrophilicity index at the LA complexes allows explaining the reverse regioselectivity experimentally observed in the presence of the  $\text{BF}_3$  and  $\text{SnCl}_4$  LA catalysts. Solvent effects are consistently predicted as marginal in the uncatalyzed mechanism because the non-polar character of the TSs. On the other hand, significant solvent effects on the reaction barriers are consistently predicted for polar TSs induced by the presence of LA catalysts. The polarity of the LA coordinated TSs in turn display high values of electrophilicity index difference.

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